REMARKS

Claims 1-48 are pending in this application. Claims 1-10 and 23-48 are withdrawn herein without prejudice or disclaimer of the subject matter contained therein. Applicants reserve the right to pursue the subject matter of these claims in a divisional or continuing application.

The Office Action dated October 3, 2007, detailed a seven-way Restriction Requirement (Groups I-VII). Applicants' previous representatives provisionally elected Group II by telephone on September 22, 2007. The Examiner withdrew claims 1-10 and 23-48 in the Office Action. Applicants hereby confirm and expressly elect Group II without traverse.

The citations to the specification included throughout this amendment are to the page or paragraph numbers of the published application (US 2005/0136122).

Claims 1-48 were rejected in the Office Action. The Office Action also objected to the abstract. Each rejection and objection is addressed individually below.

I. Objection to the Abstract

The Office Action objected to the abstract of the disclosure for being more than one paragraph and more than 25 lines. Applicants have amended the abstract herein, and respectfully request that this objection be reconsidered and withdrawn.

II. Sadozai and Naughton

Claims 11-16 were rejected as obvious under 35 U.S.C. § 103(a) in light of WO 02/09792 ("Sadozai ") and US 6,372,494 ("Naughton"). Applicants respectfully traverse.

Independent claim 11 recites:

> A method of augmenting tissue in a subject that is in need of tissue augmentation, comprising the steps of:

a) inserting a needle into a subject at a location in the subject that is in need of tissue augmentation, wherein the needle is coupled to a syringe loaded with a crosslinked HA composition that includes crosslinked, water-insoluble, hydrated HA gel particles, wherein the HA includes crosslinks represented by the following structural formula:

HA'—U—R_2—U—HA'

wherein:

each HA' is the same or different crosslinked HA' molecule;

each U is independently an optionally substituted O-acyl isourea or N-acyl urea;

and R_2 is optionally substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl aryl, heteroaryl, heterocyclyl, cycloaliphaticalkyl, aralkyl, heteroaralkyl, or heterocyclylalkyl, and

b) applying force to the syringe, whereby at least a portion of the HA composition is delivered into the subject.

Claims 12-16 depend directly or indirectly from claim 11 and add various limitations, including the addition of bioactive agents (i.e., lidocaine) to the composition.

The Office Action asserts that Sadozai "discloses composites including a biocompatible and biodegradable support comprising a water-insoluble hyaluronic acid derivative that includes an N-acyl urea that results from cross-linking .... On page 4, lines 2-3, this reference teaches a drug delivery system that can be easily injected or implanted." The Office Action further asserts that Naughton teaches a "wound healing application that uses modified cross-linked hyaluronic acids …

[and] an injectable embodiment, dispensed from syringes, for dermal augmentation and the use of lidocaine and hyaluronic acid." The Office Action opines that "[i]t would have been obvious … to combine [these] teachings … to devise a hyaluronic acid that comprises cross linked … water-insoluble hydrated hyaluronic acid gel particles and lidocaine." Finally, the Office Action asserts that "the use of hyaluronic acid for this invention is important because it is a major component of skin," and refers to the FDA's approval of Restylane without citing any references in support.

As an initial matter, the Office Action does not clearly address the method of tissue augmentation that is the subject of claims 11-22. The Office Action discusses the composition of the Sadozai HA materials, but in no way addresses why the sheets, sponges, meshes or films of Sadozai could be used in injectable applications. Sadozai makes one reference to an injectable drug delivery system (page 16, lines 10-11), but does not disclose how to make or use an injectable drug delivery system anywhere in the reference. Similarly, the Office Action points to the wound healing applications in Naughton but does not explain why it would be appropriate to include the "crosslinked, water-insoluble, hydrated HA gel particles" of the claimed invention for wound healing, let alone tissue augmentation. While the Office Action refers to the FDA's approval of Restylane for filling soft tissue defects, it provides no references for Applicants to review or assess for relevance. Applicants respectfully submit that the Office Action has not made an explicit obviousness analysis as required by *KSR*.[1]

Importantly, Sadozai and the instant claims are drawn to different, non-analogous uses of different, non-analogous materials. Sadozai discloses a composite comprising a biocompatible, biodegradable support ***and*** a hyaluronic acid ("HA") derivative that reduces ***post-operative tissue adhesion*** (page 2, lines 18-23). The composite is molded and dried or freeze-dried to form a solid implantable sponge, film, or sheet (page 11, line 23, to page 13, line 4). In contrast, the present

[1] The Supreme Court recently ruled that when performing an obviousness analysis under § 103:

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, ***this analysis should be made explicit.***

KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1740-41 (2007) (emphasis added).

application claims a method of treating subjects in need of ***tissue augmentation***, which is defined as "the subject is in need of treatment and/or correction of conditions, e.g., wrinkles, furrows and folds and other wrinkles in the skin, typically in the forehead and around the eyes, nose and lips, correction and reforming of soft tissue defects and depressed scars" (¶ 71). The instant application claims methods of tissue augmentation ***using injectable HA particles*** with or without an active agent. The claimed method delivers "a crosslinked HA composition that includes crosslinked, water-insoluble, hydrated HA gel particles" to the treatment site. Sadozai discloses implantable sponges, films, and sheets, not injectable HA particles. One of skill in the art would not use such implantable sponges, films, or sheets when developing an injection-based method of tissue augmentation.

Naughton does not address or cure the deficiencies in Sadozai. Naughton discloses a ***conditioned cell culture medium*** that may be used in a variety of wound healing applications. Although Naughton states that the conditioned medium may be formulated for eliminating wrinkles, Naughton states that this is possible because:

> The conditioned medium contains growth factors and inflammatory mediators such as, for example, VEGF, HGF, IL-6, IL-8, G-SCF and TFGβ_1 as well as extracellular matrix proteins such as type I and type III collagens, fibronectin, terascin, glycosaminoglycans, acid and basic FGF, TGF-α and TGF-β, KGF, versican, decorin and various other secreted human dermal matrix proteins which are useful in repairing physical anomalies and cosmetic defects.

(col. 25, lines 46-59). Thus Naughton relies on a broad range of growth factors and inflammatory mediators to achieve tissue augmentation, not hyaluronic acid. When used in wound healing applications, the medium can be formulated for injection with a number of different polymers or hydrogels, including cross-linked HA, as a lubricant (col. 22, line 60, to col. 23, line 4). There is no suggestion of "crosslinked, water-insoluble, hydrated HA gel particles" in the Naughton reference, nor is there any reason to use such a materials in the Naughton compositions. Thus, one skilled in the art would not consult Naughton when designing an HA-based method of tissue augmentation, as Naughton is completely unrelated to uses of HA particles, and thus is not an analogous reference for purposes of an obviousness analysis.

Furthermore, the '494 patent discloses the use of lidocaine with any formulation of the claimed conditioned media, not with an HA-based composition. Thus the '494 patent, as used in this rejection, merely stands for the proposition that lidocaine may be added to an injectable material.

The materials and their uses disclosed in Sadozai and Naughton are completely different from each other and from the claimed invention. The Office Action has not, as required by *KSR*, explicitly stated why one of skill in the art would, or even could, combine these references to created the claimed method. These references do not, alone or in combination, teach the use of cross-linked water-insoluble hydrated HA particles in a method of tissue augmentation.

Accordingly, Applicant respectfully requests that this § 103 rejection of claims 11-16 be reconsidered and withdrawn.

III. Sadozai, Radice, Szoka, and Toreki

Claims 11-12 and 17-18 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Sadozai, U.S. 6,699,471 ("Radice"), U.S. 6,593,308 ("Szoka"), and U.S. 2002/0050659 ("Toreki"). Applicants respectfully traverse.

Claim 11 is recited in Part II above. Claim 12 depends from claim 11, adding the limitation that the subject is human. Claims 17 and 18 recite:

> 17. The method of claim 12, wherein the particles have an average particle diameter distribution selected from the group consisting of a hydrated particle average diameter between about 20 μm and about 1000 μm, and a dehydrated particle average diameter between about 10 μm and about 500 μm.
>
> 18. The method of claim 17, wherein the distribution is a multimodal distribution.

The Office Action asserts that Sadozai teaches an injectable drug delivery system. The Office Action further asserts that Toreki teaches "the use of hydrated gel particles as a method to

encapsulate liquids" and "discloses hydrocapsules ranging from 100 to 25,000 micrometers." The Office Action also asserts that Szoka teaches an HA-based drug delivery system, and "the use of a multimodal program with a monodisperse particle size distribution." Applicants disagree, and respectfully note that no explanation is provided regarding how Radice may be used in an obviousness analysis for claims 11-12 and 17-18.

Sadozai is described above in Part II. Sadozai teaches sponges, films, or sheets that are composites of HA with other materials. The sponges, films, and sheets disclosed by Sadozai are not injectable.

Radice discloses the use of esterified or cross-linked HA to deliver cells via injection as a carrier liquid (col. 4, lines 11-16). The Office Action does not explain why Radice is relevant to claims 11-12 and 17-18, and thus fails to set forth an explicit analysis as required by *KSR*. Prophetic Example 13 does, however, use the phrase "tissue augmentation" in the context of treating "cutaneous malformations," such as "mastectomy or extensive burn injury of the face" (col. 23, lines 12-15). Radice states:

> Cells injected in a liquid suspension are likely to be dispersed either by vascular or lymphatic system, thus loosing [sic] the capacity of synthesizing a permanent organized extracellular matrix. A carrier system, which guarantees a temporary stable anchorage to the surrounding tissue until a permanent adhesion occurs, can be constituted by an hyaluronic acid-derivative based-formulation. In addition, hyaluronic acid may, in part, acts directly in stimulating the wound healing process, as known in the literature.

(col. 23, lines 21-30). Thus Radice teaches the injection of ***cells*** into skin to treat malformations arising from mastectomy and burns. The HA in the Radice disclosure delivers and anchors these cells to the target site. There is no teaching or disclosure of "crosslinked, water-insoluble, hydrated HA gel particles," as recited in the instant claims, nor would there be any reason to use such a material in the Radice composition, given Radice's stated use of the HA to deliver and attach cells.

Szoka discloses low molecular weight HA with a high affinity for CD44 receptors conjugated to a delivery vehicle (i.e., a liposome) with a drug (col. 2, lines 39-53), allowing for

targeted delivery of the drug from the liposome to cells with CD44 receptors (col. 3, lines 4-14). The Office Action considers Szoka to disclose the use of a "multimodal program with a monodisperse particle size distribution." Applicants disagree.

Szoka describes the use of an instrument which performs particle size analysis using a ***multimodal program*** ("[M]ean vesicle diameter [of the liposome-HA combination] as measured by dynamic light scattering ***using the multimodal program*** was 120-150 nm (SD<35% of the mean) with a monodisperse particle size distribution" (col. 16, lines 22-29) (emphasis added)). "Multimodal," as used by Szoka, refers to the program and not the particle size distribution. In fact, Szoka makes clear that its particle size distribution is ***monodisperse,*** in direct contradiction to the claimed method that uses particles that have a ***multimodal distribution.*** Furthermore, Szoka discloses a method of treating cancer (col. 3, line 62 to col. 4, line 6), not tissue augmentation. The Szoka reference is thus irrelevant and non-analogous to the instant application. One skilled in the art would not consult Szoka when designing an HA-based method of tissue augmentation, as Szoka is completely unrelated to uses of HA particles, and does not teach or suggest the recited particle sizes and size distributions.

Toreki discloses a method of making microcapsules containing a liquid core surrounded by a polymeric shell, membrane, or coating (¶ 23). The microcapsules range from 0.1 mm to 25 mm, or 100 μm to 25,000 μm. The Examples show that the microcapsules can be used to encapsulate artificial diet formulations for the mass-rearing of beneficial insects (¶ 68, 69), pest control agents (¶¶ 70-75, 77), beneficial nematodes (¶ 76), colored water (¶ 78), a mixture of sucrose and peanut oil (¶ 79), and ethylene glycol (i.e., antifreeze) (¶¶ 80-82). Neither Toreki nor the Office Action explains why one of skill in the art would seek to inject any of these materials into a subject in need of tissue augmentation, or why methods of encapsulating liquids are in any way relevant to tissue augmentation involving the application of crosslinked, water-insoluble, hydrated HA gel particles, to a treatment site.

The materials and their uses disclosed in Sadozai, Radice, Szoka, and Toreki are completely different from each other and the claimed invention, and thus non-analogous to Applicants' present

claims. The Office Action has not, as required by *KSR*, explicitly stated why one of skill in the art would, or even could, combine these references to created the claimed method. These references do not, alone or in combination, teach the use of cross-linked HA particles in a method of tissue augmentation.

Accordingly, Applicant respectfully requests that this rejection of claims 11-12 and 17-18 be reconsidered and withdrawn.

IV. Sadozai and Radice

Claims 11-12 and 19-22 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious in light of Sadozai and Radice. Applicants respectfully traverse.

Claim 11 is described above. Claim 12 adds the limitation that the subject is human. Claims 19-22 recite:

> 19. The method of claim 18, wherein the HA in the composition consists essentially of the crosslinked, water-insoluble, hydrated HA gel particles.
>
> 20. The method of claim 12, wherein the composition has at least one parameter measured at 37°C selected from a storage modulus G' of at least about 50 Pa when measured at 1 Hz frequency using a 4 cm flat geometry, and a kinematic viscosity of at least about 20,000 cPs when measured at a shear rate of 1 s^{-1}.
>
> 21. The method of claim 20, wherein the composition has a storage modulus G' of at least about 100 Pa.
>
> 22. The method of claim 21, wherein the composition has a storage modulus G' of at least about 400 Pa.

The Office Action asserts that Sadozai teaches an injectable drug delivery system that can be administered to humans, and that Radice teaches the use of injectable cross-linked HA derivatives with a viscosity of at least 350 or 400 Pa*sec^{-1}. The Office Action opines that one of skill in the art would combine these two references and arrive at Applicants' claims 11-12 and 19-22. Applicants respectfully disagree.

Sadozai and Radice are described in Parts II and III above. Sadozai teaches composites that include HA, along with other materials, and that are sponges, films, or sheets. The sponges, films, and sheets disclosed by Sadozai are not injectable.

Radice discloses the use of esterified or cross-linked HA to deliver cells via injection. Radice states "Preferred are those gels having a viscosity of at least 200 $Pa*sec^{-1}$. More preferred are gels with a viscosity of at least 250 $Pa*sec^{-1}$ or even 300 $Pa*sec^{-1}$ and most preferred are those gels having a viscosity of at least 350 $Pa*sec^{-1}$ or 400 $Pa*sec^{-1}$" (col. 10, lines 53-57).

Sadozai does not teach a method of injecting HA for tissue augmentation. Radice does not cure this deficiency for the reasons detailed in Part III above. Furthermore, Radice describes the ***viscosity*** of a cross-linked HA gel, whereas Applicants' claims are directed to a specific ***kinematic viscosity*** (or alternatively, a specific storage modulus) of cross-linked, water-insoluble, hydrated HA gel particles. These two measurements are not the same, and the Radice disclosure is irrelevant to the HA compositions having a claimed kinematic viscosity.

Furthermore, the Office Action does not provide any reason why one of skill in the art would combine the teachings of Radice with those of Sadozai. Radice teaches the viscosity of a ***liquid*** HA, while Sadozai teaches a ***solid*** implantable composite. Solids do not have viscosity, thus the teachings of Radice cannot be applied to the solid implantable composite disclosed by Sadozai. Furthermore, the treatment objectives (prevention of tissue adhesion vs. local delivery of growth factors or cells) and materials (composite including cross-linked HA vs. low molecular weight HA gels) are different. Thus Radice and Sadozai cannot be combined as asserted in the Office Action.

The materials and their uses disclosed in Sadozai and Radice are completely different from each other and the claimed invention, and thus non-analogous to Applicants' present claims. The Office Action has not, as required by *KSR*, explicitly stated why one of skill in the art would, or even could, combine these references to created the claimed method. These references do not, alone or in combination, teach the use of cross-linked HA particles in a method of tissue augmentation.

Accordingly, Applicant respectfully requests that this § 103 rejection of claims 11-12 and 19-22 be reconsidered and withdrawn.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicants hereby petition for a one month extension of time to respond to the Office Action of October 3, 2007 under 37 C.F.R. § 1.136. Please charge the $120.00 fee required under 37 C.F.R. § 1.17(a)(1) to our Deposit Account No. 08-0219. Please charge any other fees due to our Deposit Account No. 08-0219, under Order No. 0103343.00128US1 from which the undersigned is authorized to draw.

Respectfully submitted,

Dated: February 1, 2008

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